Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update.

Bibliographic Source(s)

Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, Carlesse F, Groll AH, Haeusler GM, Santolaya M, Steinbach WJ, Castagnola E, Davis BL, Dupuis LL, Gaur AH, Tissing WJE, Zaoutis T, Phillips R, Sung L. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol. 2017 Jun 20;35(18):2082-94. [129 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, Hakim H, Santolaya M, Castagnola E, Davis BL, Dupuis LL, Gibson F, Groll AH, Gaur A, Gupta A, Kebudi R, Petrilli S, Steinbach WJ, Villarroel M, Zaoutis T, Sung L. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation. Toronto (Ontario): The Hospital for Sick Children; 2012 Sep. 52 p. [199 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source

▮▮▮▮▮	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
▮▮▮▮▮	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▯	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▯	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▯	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▯▯▯	External Review
▮▮▮▯▯	Updating

Recommendations

Major Recommendations

Definitions for the levels of evidence (High, Moderate, Low, Very Low), strength of recommendations (Strong, Weak) are provided at the end of the "Major Recommendations" field.

Initial Presentation of Fever and Neutropenia (FN)

Question: What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low-risk or high-risk of poor outcomes?

Recommendation: Adopt a validated risk stratification strategy (see Table 3 in the original guideline document) and incorporate it into routine clinical management (Strong recommendation; Low-quality evidence).

Question: What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the cause of the episode and guide future treatment?

Recommendations:

Obtain blood cultures at the onset of FN from all lumens of central venous catheters (Strong recommendation; Low-quality evidence).
Consider obtaining peripheral blood cultures concurrent with central venous catheter cultures (Weak recommendation; Moderate-quality evidence).
Consider urinalysis and urine culture in patients in whom a clean-catch, midstream specimen is readily available (Weak recommendation; Low-quality evidence).
Obtain chest radiography (CXR) only in patients with respiratory signs or symptoms (Strong recommendation; Moderate-quality evidence).

Question: What empirical antibiotics are appropriate for children with high-risk FN?

Recommendations: In high-risk FN:

Use monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem as empirical therapy in pediatric high-risk FN (Strong recommendation; High-quality evidence).
Reserve the addition of a second gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (Strong recommendation; Moderate-quality evidence).

Question: In children with low-risk FN, is initial or step-down outpatient management as effective and safe as inpatient management? Is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?

Recommendations: In low-risk FN:

Consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (Weak recommendation; Moderate-quality evidence).
Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (Weak recommendation; Moderate-quality evidence).

Ongoing Management of FN Excluding Empirical Therapy

Question: When and how should the initial empirical antibiotic therapy be modified during the pediatric FN episode?

Recommendations:

In patients who are responding to initial empirical antibiotic therapy, discontinue double coverage for gram-negative infection or empirical glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (Strong recommendation; Moderate-quality evidence).
Do not modify the initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable (Strong recommendation; Low-quality evidence).
In children with persistent fever who become clinically unstable, escalate the initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria (Strong recommendation; Very low-quality evidence).

Question: When can empirical antibiotics be discontinued in patients with low- and high-risk FN?

Recommendations:

In all patients, discontinue empirical antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery (Strong recommendation; Low-quality evidence).
In patients with low-risk FN, consider discontinuation of empirical antibiotics at 72 hours in patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of

marrow recovery status, as long as careful follow-up is ensured (Weak recommendation; Moderate-quality evidence).

Empirical Antifungal Treatment

Question: What clinical parameters can classify pediatric patients with persistent FN as high-risk or low-risk of invasive fungal disease (IFD)?

Recommendation: Patients at high-risk of IFD are those with acute myeloid leukemia, high-risk acute lymphoblastic leukemia (ALL), or relapsed acute leukemia, and children undergoing allogeneic hematopoietic stem-cell transplantation (HSCT). Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high-risk of IFD. All others should be categorized as IFD low-risk (Strong recommendation; Low-quality evidence).

Question: What clinical features, laboratory tests, and imaging studies are useful to identify a fungal cause for persistent or recurrent FN despite broad-spectrum antibiotics?

Recommendations:

- In terms of biomarkers to guide empirical antifungal management for prolonged (≥ 96 hours) FN in IFD high-risk patients:
  - Consider not using serum galactomannan (GM; Weak recommendation; Moderate-quality evidence).
  - Do not use β-D-glucan (BG; Strong recommendation; Low-quality evidence).
  - Do not use fungal polymerase chain reaction (PCR) testing in blood (Strong recommendation; Moderate-quality evidence).
- In terms of imaging for the evaluation of prolonged (≥96 hours) FN in IFD high-risk patients:
  - Perform computed tomography (CT) of the lungs (Strong recommendation; Low-quality evidence).
  - Consider imaging of abdomen in patients without localizing signs or symptoms (Weak recommendation; Low-quality evidence).
  - Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms (Weak recommendation; Low-quality evidence).

Question: When should empirical antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empirical therapy?

Recommendations:

- In IFD high-risk patients with prolonged (≥96 hours) FN unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B (L-AmB) for empirical antifungal therapy (Strong recommendation; High-quality evidence).
- In IFD low-risk patients with prolonged (≥96 hours) FN, consider withholding empirical antifungal therapy (Weak recommendation; Low-quality evidence).

Definitions

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to formulate recommendations.

Quality of the Evidence

Evidence was classified as high, moderate, low or very low based upon methodological considerations and reflects confidence that the effect estimate is true. Classification is affected by limitations in study design, consistency, precision and directness.

Strength of the Recommendations

Recommendations may be strong or weak. A strong recommendation is made when benefits clearly outweigh risks or vice versa. When a strong recommendation is made, almost all patients should receive

the recommended intervention as a matter of policy. In contrast, when a weak recommendation is made, the benefits and risks of the intervention may be closely matched or there may be considerable uncertainty about the magnitude of the benefits and risks. In formulating recommendations, costs were explicitly considered in addition to benefits and risks.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Fever and neutropenia (FN)

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Oncology

Pediatrics

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To update a clinical practice guideline (CPG) for the empirical management of fever and neutropenia (FN) in children with cancer and hematopoietic stem-cell transplantation recipients

Target Population

Pediatric patients with cancer and/or undergoing hematopoietic stem cell transplantation (HSCT) who have fever and neutropenia (FN)

Interventions and Practices Considered

Diagnosis/Evaluation

- Risk stratification strategy
- Clinical, laboratory, and imaging studies
  - Blood culture
  - Urinalysis and urine culture
  - Chest radiography (CXR)
- Evaluation for invasive fungal disease (IFD)
  - Evaluation for risk factors
  - Biomarkers to guide empirical antifungal management (galactomannan [GM], β-D-glucan, polymerase chain reaction [PCR] testing) (considered but not recommended)
  - Computed tomography (CT) of the lungs and abdomen
  - Routine CT of sinuses (considered but not recommended)

Treatment/Management

- Empirical antibiotics
  - Monotherapy (antipseudomonal β-lactam, fourth-generation cephalosporin, or carbapenem)
  - Reservation of addition of a second gram-negative agent or glycopeptide, as indicated
- For low-risk fever and neutropenia (FN)
  - Initial or step-down outpatient management
  - Oral antibiotics
- Ongoing management of FN excluding antifungal therapy
  - Modification of antibiotic therapy
  - Discontinuation of empiric antibiotics if negative blood culture(s), afebrile for 24 hours, and evidence of marrow recovery
- Empirical antifungal therapy (caspofungin or liposomal amphotericin B [L-AmB])

Major Outcomes Considered

- Infection-related mortality
- Overall mortality
- Serious medical or infectious complication
- Bacteremia
- Invasive bacterial infection
- Detection of radiographic pneumonia
- Treatment failure
- Duration of fever
- Duration of antibiotics
- Duration of hospitalization
- Admission to the intensive care unit
- Critical care requirement
- Adverse events
- Readmission

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse: The International Pediatric Fever and Neutropenia Guideline Panel conducted systematic reviews of randomized trials (see the "Availability of Companion Documents" field) of interventions applied for the empirical management of pediatric fever and neutropenia (FN).

Formulating Questions and Rating Importance of Outcomes

The authors used the same key clinical questions to be addressed by the guideline and the importance of outcomes which would inform recommendations from the 2012 clinical practice guideline (CPG).

Updated Systematic Review and Meta-Analysis of the Performance of Risk Prediction Rules in Children and Young People with Febrile Neutropenia

This update review was conducted in accordance with "Systematic reviews: Centre for Reviews and Dissemination's (CRD's) guidance for undertaking reviews in health care" and registered on the PROSPERO Registry of systematic reviews: CRD42011001685. It sought studies which aimed to derive or validate a clinical decision rules (CDR) in children or young people (aged 0–18 years) presenting with febrile neutropenia (FN). Both prospective and retrospective cohorts were included, but those using a case-control ("two-gate") approach were excluded as these have been previously shown to exaggerate diagnostic accuracy estimates.

Search Strategy and Selection Criteria

The electronic search strategy was reviewed and repeated on the following databases from February 2009 to September 2011:

MEDLINE
MEDLINE In-Process & Other Non-Indexed Citations
EMBASE
CINAHL
Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS)

Reference lists of relevant systematic reviews and included articles were reviewed for further relevant articles. Published and unpublished studies were sought and no language restrictions applied. Non-English language studies were translated. Two reviewers independently screened the title and abstract of studies for inclusion, and then the full text of retrieved articles. Disagreements were resolved by consensus.

The search was updated to include articles indexed as of 2 March 2016.

Systematic Review and Meta-analysis of the Discriminatory Performance of Risk Prediction Rules in Febrile Neutropaenic Episodes in Children and Young People

The review was conducted in accordance with "Systematic reviews: CRD's guidance for undertaking reviews in health care" and registered on the Health Technology Assessment (HTA) Registry of systematic reviews: CRD32009100453. It sought studies which aimed to derive or validate a CDR in children or young people (aged 0– 18 years) presenting with febrile neutropaenia. Both prospective and retrospective

cohorts were included, but those using a case–control ("two-gate") approach were excluded as these have been previously shown to exaggerate diagnostic accuracy estimates. Studies exclusively addressing the prediction of radiologically confirmed pneumonia are subject to a separate review.

Search Strategy and Selection Criteria

An electronic search strategy (see Web Appendix 1 in the systematic review) was developed which examined the following databases from their inception to February 2009:

MEDLINE
MEDLINE In-Process and Other Non-Indexed Citations
EMBASE
CINAHL
Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Health Technology Assessment Database (HTA)
Cochrane Central Register of Controlled Trials (CENTRAL)
Conference Proceedings Citation Index - Science (CPCI-S)
Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS)

Reference lists of relevant systematic reviews and included articles were reviewed for further relevant articles. Published and unpublished studies were sought and no language restrictions applied. Non-English language studies were translated. Two reviewers independently screened the title and abstract of studies for inclusion, and then the full text of retrieved articles. Disagreements were resolved by consensus.

The search was updated to include articles indexed as of 2 March 2016.

Utility of Peripheral Blood Cultures in Patients with Cancer and Suspected Blood Stream Infections: a Systematic Review

Data Sources and Searches

An electronic search of OVID Medline (1980 to October 13, 2011), EMBASE (1980 to October 13, 2011), and the Cochrane Central Register of Controlled Trials (from inception until third quarter, 2011) was performed. The search terms included peripheral blood culture, venipuncture, central venous line, central venous catheter, bacteremia, and neoplasms (see Appendix 1 in the systematic review). The authors included all trial types and languages, but limited the search to studies published after 1980 as studies published prior to then were considered less relevant given changes in supportive care over time. Changes in supportive care over time include indications for central venous lines (CVL), approach to empiric antibiotic therapy, practices related to antibacterial and antifungal prophylaxis, and changing epidemiology of infections in patients with cancer. The review was registered in PROSPERO, the international database of prospectively registered systematic reviews in health and social care (CRD42011001610).

Study Selection

Inclusion and exclusion criteria were defined before the search was conducted. Inclusion criteria were (1) population consisted solely of patients of any age with cancer or hematopoietic stem cell transplantation (HSCT), (2) evaluated concurrent peripheral and CVL cultures, and (3) reported sufficient data to permit calculation of the primary outcome (proportion of bacteremia detected only by the peripheral blood [PB] culture). The only exclusion criterion was duplicate publication. There was no restriction by language. One reviewer evaluated all the titles and abstracts identified by the search strategy, and any potentially relevant publication was retrieved in full. The authors also identified potential articles through review of references and perusal of personal files. Two independent reviewers then assessed the full articles for study eligibility. The final set of included studies was determined by agreement of both reviewers.

The search was updated to include articles indexed as of 29 February 2016.

Systematic Review and Meta-analysis of the Value of Clinical Features to Exclude Radiographic Pneumonia in Febrile Neutropenic Episodes in Children and Young People

The review was conducted in accordance with "Systematic reviews: CRD's guidance for undertaking reviews in health care." In keeping with recent recommendations, the protocol was registered with the HTA Registry of systematic reviews, CRD32009100453.

Search and Retrieval Strategy

An electronic search strategy (see the Web Appendix in the systematic review [see the "Availability of Companion Documents" field]) was developed, which examined the following databases from inception until February 2008:

MEDLINE
MEDLINE(R) In-Process and Other Non-Indexed Citations
EMBASE
CINAHL
Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Health Technology Assessment Database (HTA)
Cochrane Central Register of Controlled Trials (CENTRAL)
Conference Proceedings Citation Index – Science (CPCI-S)
Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS)

Reference lists of relevant systematic reviews and included articles were screened for further relevant studies. Published and unpublished reports were sought and no language restrictions were applied.

Inclusion and Exclusion Criteria

Studies were included in the review if they met the following criteria:

Methodology

Cohort studies, with prospective or retrospective collection of patients. Studies using a case–control ("two-gate") approach were excluded as these have previously been shown to grossly exaggerate diagnostic accuracy estimates.

Population

Children or young people (aged 0–18 years) who were receiving treatment for cancer or leukaemia (including extra-cranial and intra-cranial tumours) presenting with febrile neutropenia.

Predictor Variables

Clinical examination findings (for example cough, raised respiratory rate or rhonchi).

Outcomes

Radiographically diagnosed pneumonia.

Study Selection

Two reviewers independently selected articles for inclusion by screening the title and abstract, and where appropriate, the full text of retrieved articles. Disagreements were resolved by consensus.

The search was updated to include articles indexed as of 2 March 2016.

Strategies for Empiric Management of Pediatric Fever and Neutropenia in Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: A Systematic Review of Randomized Trials

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations for reporting.

Data Sources and Searches

The authors used the Ovid SP platform (Ovid, New York, NY) to search MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials and the National Center for Biotechnology Information platform to search PubMed for articles indexed up to September 25, 2015. The search strategy included the Medical Subject Heading terms and text words that identified children and adolescents with FN among those with cancer or who received HSCT (the Data Supplement in the systematic review contains the full search strategy). The set was limited to randomized trials published in 1980 or more recently. There was no restriction by language.

Study Selection

Inclusion and exclusion criteria were defined a priori. Studies were included if patients were children or adolescents with cancer or who had received HSCT; if the publication was a fully published primary randomized or quasi-randomized trial; and if the study evaluated an intervention directly related to the management of FN. Reasons for excluding studies were as follows: not a full-text publication; not a randomized or quasi-randomized trial; did not involve pediatric patients (age <25 years); less than 50% of patients had cancer or were undergoing HSCT; evaluated prophylactic intervention; and intervention consisted of different anticancer treatment strategies in which FN was an outcome.

Two reviewers independently evaluated the titles and abstracts of publications identified by the search strategy, and any potentially relevant publication was retrieved in full. Final inclusion of studies into the systematic review was by agreement of both reviewers. Agreement of study inclusion between the two reviewers was evaluated using the k statistic, and agreement was defined as slight (0% to 20%), fair (21% to 40%), moderate (41% to 60%), substantial (61% to 80%), or almost perfect (81% to 100%).

The search was updated to include articles indexed as of 24 October 2016.

Note: Additionally, systematic reviews were done for urinalysis and urine culture and imaging for invasive fungal disease (IFD). Refer to the guideline supplement (see the "Availability of Companion Documents" field) for additional information.

Number of Source Documents

Note from the National Guideline Clearinghouse: The International Pediatric Fever and Neutropenia Guideline Panel conducted systematic reviews of randomized trials (see the "Availability of Companion Documents" field) of interventions applied for the empirical management of pediatric fever and neutropenia (FN).

Updated Systematic Review and Meta-Analysis of the Performance of Risk Prediction Rules in Children and Young People with Febrile Neutropenia

Nine articles reporting on 8 studies were eligible for inclusion in the review. See Figure 1 in the systematic review for a flow chart detailing the study selection process.

Systematic Review and Meta-analysis of the Discriminatory Performance of Risk Prediction Rules in Febrile Neutropaenic Episodes in Children and Young People

Twenty-one articles reporting on 20 studies were eligible for inclusion in the review. See Figure 1 in the systematic review for a flow chart detailing the study selection process.

Utility of Peripheral Blood Cultures in Patients with Cancer and Suspected Blood Stream Infections: a Systematic Review

The authors identified 149 titles and abstracts from their search, and 29 full articles were retrieved for detailed evaluation. Seven studies were included in the meta-analysis. See Figure 1 in the systematic review for a flow chart detailing the study selection process.

Systematic Review and Meta-analysis of the Value of Clinical Features to Exclude Radiographic Pneumonia

in Febrile Neutropenic Episodes in Children and Young People

A total of 2,057 articles were identified from electronic searches, and 3 further articles were identified from examining systematic reviews and the bibliographies of included studies. From this, 89 articles were identified for detailed examination, of which 4 articles were eligible for inclusion in this review and 21 further studies were incorporated into a separate systematic review of clinical decision rules. See Figure 1 in the systematic review for a flow chart detailing the study selection process.

Strategies for Empiric Management of Pediatric Fever and Neutropenia in Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: a Systematic Review of Randomized Trials

There were 11,469 unique citations identified by the search strategy, of which 196 were retrieved for full-text evaluation. Of these citations, 68 met the eligibility criteria and were included in the systematic review. See Figure 1 in the systematic review for a flow chart detailing the study selection process.

Note: Additionally, systematic reviews were done for urinalysis and urine culture and imaging for invasive fungal disease (IFD). Refer to the guideline supplement (see the "Availability of Companion Documents" field) for additional information.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of the Evidence

Evidence was classified as high, moderate, low or very low based upon methodological considerations and reflects confidence that the effect estimate is true. Classification is affected by limitations in study design, consistency, precision and directness.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse: The International Pediatric Fever and Neutropenia Guideline Panel conducted systematic reviews of randomized trials (see the "Availability of Companion Documents" field) of interventions applied for the empirical management of pediatric fever and neutropenia (FN).

Updated Systematic Review and Meta-Analysis of the Performance of Risk Prediction Rules in Children and Young People with Febrile Neutropenia

Validity Assessment and Data Extraction

The validity of each study was assessed as with the previous review using 11 of the 14 questions from the quality assessment tool for diagnostic accuracy studies (QUADAS).

Data were extracted by one reviewer and checked by the other. The data extracted included age and sex distribution of the included participants, geographical location of the study, the participant inclusion/exclusion criteria, and the performance of the clinical decision rules (CDR) as a 2*k table (where k refers to the number of strata described) or as sensitivity/specificity, as well as aspects of the methods

used to derive the CDR (where applicable).

Methods of Analysis/Synthesis

Where possible, data from new publications were added to meta-analyses undertaken in the original review. Quantitative synthesis was undertaken when more than 2 studies tested the same CDR, and where appropriate, was investigated for sources for heterogeneity. For this update review, only dichotomous test data were found. For CDR with 3 datasets, a univariate approach was used (pooling sensitivity and specificity separately). For those with 4 or more, a bivariate model was fitted using 'metandi' in STATA10. The protocol specified a random-effects meta-analysis was undertaken using WinBUGS 1.4.3 for tests with 3 or more risk strata, but no data were found eligible for this analysis.

Heterogeneity between study results was explored through consideration of study populations, study design, CDR and outcomes chosen, although the small number of studies in each category limited this approach. Sensitivity analysis was undertaken by comparing results when the original (derivation) data set was included and excluded. For those areas where a quantitative synthesis was not possible, a narrative approach was used.

Systematic Review and Meta-analysis of the Discriminatory Performance of Risk Prediction Rules in Febrile Neutropaenic Episodes in Children and Young People

Validity Assessment and Data Extraction

The validity of each study was assessed using 11 of the 14 questions from the QUADAS assessment tool for diagnostic accuracy studies. The QUADAS tool was adapted specifically for the review, omitting questions on 'time between index and reference test', 'intermediate results' and 'explanation of withdrawals' (see Web Appendix 2 in the systematic review). The CDR and reference tests are necessarily related, and the design of a CDR means that 'intermediate' results are included in any analysis. The issue of incomplete data was addressed in the analysis of the method of derivation or validation, and as such was not included as a quality criterion.

Data were extracted by one reviewer and checked by the other. The data extracted included age and sex distribution of the included participants, geographical location of the study and participant inclusion/exclusion criteria. The performance of the CDR as a 2*k table (where k refers to the number of strata described) as well as the methods used to derive the CDR (where applicable), the variables considered, methods of statistical analysis and approach to multiple episodes in individual patients and missing data were also extracted.

Methods of Analysis/Synthesis

Quantitative synthesis was undertaken for studies which tested the same CDR and, where appropriate, was investigated for sources for heterogeneity.

For dichotomous test data, analyses were attempted with a bivariate model (using 'metandi' in STATA10). For tests with very small numbers of studies to pool (n = 4) fitting a bivariate model is problematic as the procedure frequently fails to converge. In these cases, a univariate approach was used (pooling sensitivity and specificity separately).

For tests where three-level (low, medium and high risk) results were produced, an approach based on a previous meta-analysis of three-level CDR results was used. This random-effects meta-analysis was undertaken using WinBUGS 1.4.3 to estimate the proportions of individuals classified as low, medium or high risk in the bacteraemic and non-bacteraemic groups. As an extension to this method, bivariate random effects were applied to the calculation of each proportion. Data from studies which used a similar rule but provided only two of the risk categories (i.e. low versus medium–high) were also included in this analysis. These proportions were used to calculate likelihood ratios (LR) for each risk category and the corresponding 95% credible intervals (CrI).

Heterogeneity between study results was explored through consideration of study populations, study design, predictor variables assessed and outcomes chosen, although the small number of studies in each

category limited this approach. Sensitivity analysis was undertaken by comparing results when the original (derivation) dataset was included and excluded.

For those areas where a quantitative synthesis was not possible, a narrative approach was used.

Utility of Peripheral Blood Cultures in Patients with Cancer and Suspected Blood Stream Infections: a Systematic Review

Data Extraction

The data extracted from the studies were as follows: patient age, population description, cancer type, central venous line (CVL) type, definition of contaminant, definition of bacteremia, technique for blood culture acquisition, time between the PB and CVL cultures, volume of blood cultures, number of patients with neutropenia (absolute neutrophil count ≤500/μL), care location, and the proportion of the study population with bacteremia. The primary outcome was the proportion of bacteremia detected only by the peripheral blood (PB) culture. The secondary outcomes were (1) proportion of bacteremia detected only by the CVL culture, (2) rate of contaminant from the PB culture, and (3) rate of contaminant from the CVL culture. The authors also determined if a study removed likely contaminants from the reported rate of bacteremia.

Study quality was evaluated with a modified version of an instrument previously developed to describe quality in studies of prognosis. Four sources of potential bias were examined using this instrument: study participation, study attrition, confounding variables, and measurement of outcomes. Studies were each rated as having low, medium, or high risk of bias with respect to each element.

Statistical Analysis

Outcomes were reported as proportions. For synthesis, the authors combined the proportion of samples identified by site of culture, classifying these as either peripheral-alone, central-alone, or both sites. They undertook meta-analysis using logit transformation of the proportions, in a random-effects meta-analysis, fitting this with the METAFOR package in R. Subgroups were explored as covariates in the model, taking $P<0.05$ as significant.

Systematic Review and Meta-analysis of the Value of Clinical Features to Exclude Radiographic Pneumonia in Febrile Neutropenic Episodes in Children and Young People

Data Extraction

Data were extracted by one reviewer using a standardised data extraction form and checked by the second. Disagreements were resolved by consultation with a third reviewer. The data extracted included participant age, geographical location of the study, the participant inclusion/exclusion criteria, and a two by two table summarising the performance of clinical examination for predicting radiographic pneumonia (for calculating sensitivity and specificity).

Methods of Analysis/Synthesis

Where possible, quantitative synthesis (meta-analysis) was undertaken and random-effects models were used to account for between-study heterogeneity in summary results. To assess the accuracy of clinical features for predicting radiographic pneumonia, meta-analyses were initially attempted using a bivariate model so as to account for between-study correlation in sensitivity and specificity (using the 'metandi' command for STATA1013). However, given the small number of studies identified this model would not converge, and so a separate univariate random-effects meta-analysis was performed to obtain average estimates of sensitivity and specificity, their 95% confidence intervals (CIs) and 95% prediction intervals for the sensitivity and specificity in a new study; the latter helps describe how the heterogeneity may cause diagnostic accuracy in an individual study to vary from the average accuracy. Results for the individual studies and the meta-analyses were plotted in receiver operator curve (ROC) space.

Heterogeneity in results was estimated and accounted for using the random-effects meta-analysis framework, and it was expected *a priori* due to the small number of studies and the expected differences

in study populations, quality and design. Sensitivity analysis was undertaken by comparing meta-analysis results when outlying studies were omitted.

Strategies for Empiric Management of Pediatric Fever and Neutropenia in Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: a Systematic Review of Randomized Trials

Validity Assessment

The validity of each study was assessed using 11 of the 14 questions from the QUADAS assessment tool for diagnostic accuracy studies. The QUADAS tool was developed to measure the methodological quality of diagnostic accuracy studies in systematic reviews. The tool is generic and is intended to be modified to fit the particular situation of the clinical question under study. In this setting, the adaptation led to omitting questions on 'time between index and reference test', 'intermediate results' and 'explanation of withdrawals'. These questions were removed as there is no clinically significant lag between examination and admission radiography, and 'intermediate' and incomplete results (for example, cases where not all clinical features were recorded) were included in the analysis.

Data Abstraction and Methodologic Approach

Two reviewers abstracted all data in duplicate, and any discrepancies were resolved by consensus. An important outcome in studies of FN is treatment failure. Criteria used to define failure varied widely between studies, but common themes included persistent fever, progressive infection, breakthrough or new infection, and infection-related mortality. Some studies included modification of the initial antibiotic regimen as a criterion for failure, and thus, the authors used two approaches to define failure in this review. The primary outcome was treatment failure in which modification of the antibiotic regimen was included as a criterion for failure. Secondary outcomes were treatment failure in which antibiotic modification was not included as a failure criterion, infection-related mortality, overall mortality, duration of fever, duration of antibiotics, duration of hospitalization, admission to the intensive care unit, and adverse events.

Study-level factors collected included years of study publication and enrollment, country of study conduct, sponsor of trial, age range, patient population (cancer, HSCT, or both), antibiotic prophylaxis, and FN risk status (defined by each study). Intervention characteristics included details of the randomized intervention, which varied by the specific intervention type.

Interventions Evaluated

On the basis of the available randomized trials and clinical relevance, two broad types of comparisons were made, namely different antibiotic combinations as empirical therapy and management strategies other than empirical antibiotic therapy choice. To identify optimal empirical antibiotic approaches, the authors first compared monotherapy versus aminoglycoside containing combination therapy. Studies restricted to low-risk FN were excluded from this comparison. Only monotherapy regimens that were considered appropriate for high-risk FN based on spectrum of activity from our original guideline were included. Appropriate regimens were an antipseudomonal β-lactam (such as piperacillin-tazobactam or ticarcillin-clavulanic acid), an antipseudomonal cephalosporin (such as cefepime), or a carbapenem (such as meropenem or imipenem). Ceftazidime and ceftriaxone monotherapy were not recommended and were therefore not included in this analysis. Different monotherapy regimens evaluated were an antipseudomonal penicillin with or without a β-lactamase inhibitor versus a fourth-generation cephalosporin (such as cefepime) and a carbapenem versus a fourth-generation cephalosporin.

Other management strategies evaluated were treatment setting, route of antibiotic administration, and therapeutic colony-stimulating factor (CSF) administration. Evaluation of inpatient versus outpatient management was not restricted to studies in which antibiotic regimen and route of administration were the same between the randomized arms. Both initial and step-down outpatient management trials were included as outpatient regimens. In contrast, studies that randomly assigned between intravenous and oral route of antibiotic administration were restricted to studies that provided these interventions in the same setting, whether the setting was inpatient, outpatient, or a step-down strategy. Both initial oral and step-down oral management trials were included as oral regimens. This approach was taken to

ensure that a specific study would only be included in one of these two analyses (setting or route of administration) and not both. Trials that randomly assigned patients with FN episodes to receive or not receive CSFs were restricted to the therapeutic setting where CSF administration was initiated at the onset of an episode of FN.

Assessment of Study Quality

Two reviewers assessed study quality, and any discrepancies were resolved by consensus. The authors used the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. This tool includes the following domains relevant to internal validity: selection bias, performance bias, detection bias, attrition bias, and reporting bias. They evaluated the following sources of bias related to these domains: random number generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

Statistical Methods

The authors combined data at the study level for this meta-analysis. Synthesis was conducted when there were at least three studies that reported an outcome for a given comparison. For dichotomous outcomes such as FN failure rate, data were synthesized using the risk ratio (RR) as the effect measure with its 95% CI. For continuous outcomes with missing summary measures, we made the following assumptions to facilitate data synthesis: the mean can be approximated by the median, and the range contains six standard deviations. Continuous outcomes were synthesized using the weighted mean difference (MD). Effect sizes of dichotomous and continuous outcomes were weighted by the Mantel-Haenszel and inverse variance methods, respectively. Because they anticipated heterogeneity between studies, a random effects model was used for all analyses. Statistical heterogeneity between trials was assessed using the I^2 value, which describes the percentage of total variation across studies as a result of heterogeneity rather than chance.

Potential publication bias was explored by visual inspection of funnel plots when at least 10 studies were available. Stratified analysis and meta-regression were not conducted given the number of randomized trials available for each intervention. Synthesis was conducted using Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). Descriptive analysis of included studies was conducted using the SAS statistical program (SAS-PC, version 9.4; SAS Institute, Cary, NC).

Note: Additionally, systematic reviews were done for urinalysis and urine culture and imaging for invasive fungal disease (IFD). Refer to the guideline supplement (see the "Availability of Companion Documents" field) for additional information.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The International Pediatric Fever and Neutropenia Guideline Panel includes representation from pediatric oncology, infectious diseases, nursing, and pharmacy, as well as a patient advocate and a guideline methodologist from 10 different countries.

The methodology applied to the clinical practice guideline (CPG) update mirrored the 2012 Fever and Neutropenia (FN) clinical practice guideline (CPG). The guideline authors followed previously validated procedures for creating evidence-based guidelines and used the Appraisal of Guidelines for Research & Evaluation II instrument as a framework. The Grading of Recommendations Assessment, Development and Evaluation approach was used to generate recommendations. Details of methodology may be found in the Data Supplement.

Members were divided into working groups that focused on the three major sections addressed in the

initial CPG: initial presentation, ongoing management, and empirical antifungal therapy. Given the paucity of pediatric data at the time of initial CPG development, none of the original systematic reviews were restricted to randomized controlled trials (RCTs). For the guideline update, the authors decided to focus on pediatric RCTs for questions related to therapy because they believed that clinical practice was unlikely to change on the basis of additional observational studies alone. For questions related to risk stratification and evaluation, the original systematic reviews were updated.

Establishment of the Guideline Panel

The 2012 guideline Panel was revised and constituency included representation by discipline, nation and a patient advocate. Experts were chosen based upon publication history in supportive care or fever and neutropenia (see Appendix 1 in the guideline supplement [see the "Availability of Companion Documents" field]).

Panel Meeting and Development of Recommendations

Evidence was reviewed and recommendations were debated in a series of conference calls. The panel met face-to-face in New Orleans, Louisiana on October 30, 2016. Iterations of each section and then the final overall CPG were circulated until all authors agreed with its content.

Rating Scheme for the Strength of the Recommendations

Strength of the Recommendations

Recommendations may be strong or weak. A strong recommendation is made when benefits clearly outweigh risks or vice versa. When a strong recommendation is made, almost all patients should receive the recommended intervention as a matter of policy. In contrast, when a weak recommendation is made, the benefits and risks of the intervention may be closely matched or there may be considerable uncertainty about the magnitude of the benefits and risks. In formulating recommendations, costs were explicitly considered in addition to benefits and risks. For some recommendations, level of evidence was down-graded from the previous fever and neutropenia (FN) clinical practice guideline (CPG) to the current version. This adjustment occurred to better standardize how level of evidence was applied across sections.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A final revised version was not sent to external experts prior to submission for publication as the Panel contained much pediatric fever and neutropenia (FN) expertise. Instead, the Panel used the peer-review process during manuscript submission as a rigorous and efficient approach to external review.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation

Refer to the "Literature update and analysis" sections of the original guideline document for specific benefits.

Potential Harms

Adverse effects associated with treatment

Refer to the "Literature update and analysis" sections of the original guideline document for specific harms.

Implementation of the Guideline

Description of Implementation Strategy

Implementation is an important issue, and national and international guidance will be important to effect change. Adaptation will be required at the institutional level to delineate specific rather than generic antibiotic choices and to decide whether to implement or not implement weak recommendations. Decision-making for weak recommendations could also be made at the specific provider or patient level. Cost-effectiveness studies may be relevant when deciding whether to implement weak recommendations.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, Carlesse F, Groll AH, Haeusler GM, Santolaya M, Steinbach WJ, Castagnola E, Davis BL, Dupuis LL, Gaur AH, Tissing WJE, Zaoutis T, Phillips R, Sung L. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol. 2017 Jun 20;35(18):2082-94. [129 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

International Pediatric Fever and Neutropenia Guideline Group - International Agency

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Guideline Committee

International Pediatric Fever and Neutropenia Guideline Panel

Composition of Group That Authored the Guideline

Panel Members: Thomas Lehrnbecher, Hospital for Children and Adolescents, Johann Wolfgang Goethe University, Frankfurt; Andreas H. Groll, University Children's Hospital, Muenster, Germany; Paula Robinson, Pediatric Oncology Group of Ontario; Sarah Alexander, Hospital for Sick Children, Toronto, Ontario, Canada; L. Lee Dupuis, Hospital for Sick Children, Toronto, Ontario, Canada; Lillian Sung, The Hospital for Sick Children, Toronto, Ontario, Canada; Brian Fisher, Children's Hospital of Philadelphia, Philadelphia, PA; Theo Zaoutis, Children's Hospital of Philadelphia, Philadelphia, PA; Roland A. Ammann, Bern University Hospital, University of Bern, Switzerland; Melissa Beauchemin, Columbia University/Herbert Irving Cancer Center, New York, NY; Fabianne Carlesse, Pediatric Oncology Institute, GRAACC/Federal University of Sao Paulo, Sao Paulo, Brazil; Gabrielle M. Haeusler, Peter MacCallum Cancer Centre, Melbourne, Monash Children's Hospital, Clayton, Victoria, Australia; Maria Santolaya, Hospital Luis Calvo Mackenna, Universidad de Chile, Santiago, Chile; William J. Steinbach, Duke University Medical Center, Durham, NC; Elio Castagnola, Istituto Giannina Gaslini, Genova, Italy; Bonnie L. Davis, High Tor Limited, Nassau, Bahamas; Aditya H. Gaur, St Jude Children's Research Hospital, Memphis, TN; Wim J.E. Tissing, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; Robert Phillips, Leeds Teaching Hospital, NHS Trust, Leeds, University of York, York, United Kingdom

Financial Disclosures/Conflicts of Interest

Each member completed conflict of interest forms and no conflicts precluded involvement in the Panel.

The guideline was editorially independent from the funding body (Canadian Institutes of Health Research and Garron Comprehensive Cancer Centre).

Authors' Disclosures of Potential Conflicts of Interest

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to https://www.asco.org/rwc or https://ascopubs.org/jco/site/ifc.

Thomas Lehrnbecher
Consulting or Advisory Role: Gilead Sciences, Merck/Merck Sharp & Dohme, Astellas Pharma
Speakers' Bureau: Astellas Pharma, Gilead Sciences
Research Funding: Gilead Sciences
Travel, Accommodations, Expenses: Astellas Pharma

Paula Robinson
No relationship to disclose

Brian Fisher
Research Funding: Pfizer (Inst), Merck (Inst), Ansun BioPharma (Inst)

Sarah Alexander
No relationship to disclose

Roland A. Ammann
Travel, Accommodations, Expenses: EUSA Pharma

Melissa Beauchemin
No relationship to disclose

Fabianne Carlesse
Speakers' Bureau: Astellas, United Medical, Pfizer

Andreas H. Groll
Consulting or Advisory Role: Astellas Pharma, Basilea, Gilead Sciences, Merck Sharp & Dohme, Schering-Plough, Zeneus/Cephalon
Speakers' Bureau: Astellas Pharma, Basilea, Gilead Sciences, Merck Sharp & Dohme, Schering-Plough, Zeneus/Cephalon, Pfizer
Research Funding: Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering-Plough

Gabrielle M. Haeusler
No relationship to disclose

Maria Santolaya
No relationship to disclose

William J. Steinbach
Consulting or Advisory Role: Gilead Sciences, Merck
Research Funding: Astellas Pharma

Elio Castagnola
Consulting or Advisory Role: Basilea, Astellas Pharma, Pharmaceutica, Gilead Sciences, Pfizer
Travel, Accommodations, Expenses: Pfizer

Bonnie L. Davis
No relationship to disclose

L. Lee Dupuis

Consulting or Advisory Role: Jazz Pharmaceuticals
Research Funding: Jazz Pharmaceuticals

Aditya H. Gaur
Research Funding: Gilead Sciences (Inst)

Wim J.E. Tissing
No relationship to disclose

Theo Zaoutis
Consulting or Advisory Role: Napriva
Research Funding: Merck (Inst)

Robert Phillips
No relationship to disclose

Lillian Sung
No relationship to disclose

Guideline Endorser(s)

American Society of Clinical Oncology - Medical Specialty Society

American Society of Pediatric Hematology/Oncology - Professional Association

C17 Council - Professional Association

Children's Oncology Group - Medical Specialty Society

Multinational Association of Supportive Care in Cancer - Disease Specific Society

Pediatric Oncology Group of Ontario - Professional Association

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, Hakim H, Santolaya M, Castagnola E, Davis BL, Dupuis LL, Gibson F, Groll AH, Gaur A, Gupta A, Kebudi R, Petrilli S, Steinbach WJ, Villarroel M, Zaoutis T, Sung L. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation. Toronto (Ontario): The Hospital for Sick Children; 2012 Sep. 52 p. [199 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site .

Availability of Companion Documents

The following are available:

Lehrnbecher T et al.Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. Data supplement. 2017. 25 p. Available from the Journal of Clinical Oncology Web site .
Phillips RS, Lehrnbecher T, Alexander S, Sung L. Updated systematic review and meta-analysis of the

performance of risk prediction rules in children and young people with febrile neutropenia. PLoS One. 2012 May;7(5):e38300. Available from the PLOS One Web site .
Phillips B, Wade R, Stewart LA, Sutton AJ. Systematic review and meta-analysis of the discriminatory performance of risk prediction rules in febrile neutropaenic episodes in children and young people. Eur J Cancer. 2010 Nov;46(16):2950-64. Available from the European Journal of Cancer Web site .
Rodríguez L, Ethier M-C, Phillips B, Lehrnbecher T, Doyle J, Sung L. Utility of peripheral blood cultures in patients with cancer and suspected blood stream infections: a systematic review. Support Care Cancer. 2012 Dec;20(12):3261-7. Available from the Supportive Care in Cancer Web site .
Phillips B, Wade R, Westwood M, Riley R, Sutton AJ. Systematic review and meta-analysis of the value of clinical features to exclude radiographic pneumonia in febrile neutropenic episodes in children and young people. J Pediatr Child Health. 2012 Aug;48(8):641-8. Available to subscribers from the Journal of Pediatric and Child Health Web site .
Robinson PD, Lehrnbecher T, Phillips R, Dupuis LL, Sung L. Strategies for empiric management of pediatric fever and neutropenia in patients with cancer and hematopoietic stem-cell transplantation recipients: a systematic review of randomized trials. J Clin Oncol. 2016 Jun 10;34(17):2054-60. Available from the Journal of Clinical Oncology Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on January 8, 2013. The information was verified by the guideline developer on January 28, 2013. This NGC summary was updated by ECRI Institute on October 2, 2017. The updated information was not verified by the guideline developer.

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